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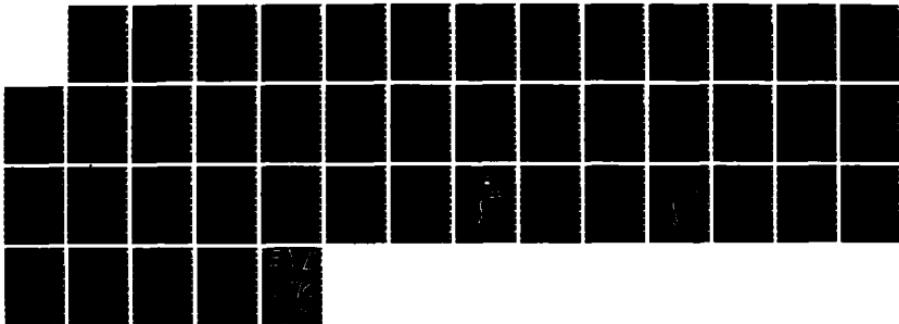
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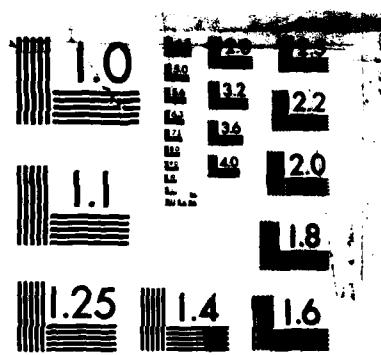
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PREPARATION AND PURIFICATION OF MULTIGRAM QUANTITIES OF TAX AND SEX

THIRD PHASE FINAL REPORT

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) This final report describes the multigram preparation and purification of 1-acetylhexahydro-3,5-dinitro-1,3,5-triazine (TAX) and the feasibility of preparing, purifying, and analyzing multigram quantities of 1-acetylloctahydro-3,5,7-trinitro-1,3,5,7-tetrazocine (SEX) needed for toxicological testing. TAX was prepared by nitrolysis of 1,3,5-triacetylhexahydro-1,3,5-triazine (TRAT) using a mixture of trifluoroacetic anhydride (TFAA) and 100% nitric acid.		

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1-Acetylhexahydro-3,5-dinitro-1,3,5-triazine (TAX)
1,3,5,7-Tetraacetyloctahydro-1,3,5,7-tetrazocine (TAT)
1,3,5-Triacetylhexahydro-1,3,5-triazine (TRAT)

20. (Continued)

A continuous plug-flow reactor design was found to be a rapid, efficient, and safe method for the preparation of TAX in kilogram quantities. The crude TAX, contaminated with 25% to 30% RDX, was obtained analytically pure (99.9%) by high-pressure liquid chromatography (HPLC) on silica gel using nitromethane as the eluent.

SEX was prepared by nitrolysis of 1,5-diacetyloctahydro-3,7-dinitro-1,3,5,7-tetrazocine (DADN), using a mixture of 30% oleum and 100% nitric acid. Conditions for the preparation of the DADN/SEX/HMX mixture were optimized and the process can be conducted batchwise. Thus SEX could be provided in the quantities desired for subsequent purification.

The crude SEX was contaminated with up to 5% HMX and up to 20% DADN, depending on the reaction conditions. Removal of the DADN contamination was accomplished through open hot column chromatography (90-100°C) on silica gel with a nitromethane eluent. This yielded SEX in greater than 95% purity. The resulting SEX/HMX mixture could be purified to greater than 98% SEX by recrystallization from acetone.

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SUMMARY

This final report describes the synthesis and purification of 3 kg of 1-acetylhexahydro-3,5-dinitro-1,3,5-triazine (TAX) and the feasibility of producing kilogram quantities of 1-acetyloctahydro-3,5,7-trinitro-1,3,5,7-tetrazocine (SEX). The objectives were to (1) prepare and purify 3 kg of TAX; (2) establish the technical feasibility of producing kilogram quantities of SEX needed for toxicological testing, in satisfactory purity and with proper analytical characterization of residual impurities; (3) demonstrate the feasibility of the synthesis approach on a one-pound batch reaction; and (4) provide a cost-plus-fixed-fee estimate for preparing additional quantities of SEX.

Kilogram quantities of TAX, contaminated with RDX, were prepared by nitrolysis of 1,3,5-triacetylhexahydro-1,3,5-triazine (TRAT), using a mixture of trifluoroacetic anhydride and 100% nitric acid. The crude TAX, contaminated with 30% to 40% RDX, was purified by high pressure liquid chromatography (HPLC) on prepacked silica gel columns, using a nitromethane eluent. This purification procedure yielded TAX of purity greater than 99.9%, as determined by analytical HPLC.

SEX was prepared by nitrolysis of 1,5-diacetyloctahydro-3,7-dinitro-1,3,5,7-tetrazocine (DADN), using a mixture of 30% oleum and 100% nitric acid. The crude SEX was contaminated with 2% to 5% HMX and 15% to 20% DADN. This composition of material was achieved with 10- to 500-gram batch reactions.

Analytically pure SEX (98+%) was obtained through the following procedure. Open hot-column chromatography (90°-100°C) on silica gel with a nitromethane eluent was used to remove the DADN contamination. The resulting SEX/HMX mixture was separated to yield 99+% SEX by preparative HPLC on prepacked silica gel columns, again using a nitromethane eluent. Alternatively, repeated recrystallizations of the SEX/HMX-mixtures from acetone yielded 98+% SEX, contaminated with 1% to 2% HMX and only trace quantities of DADN.

A cost estimate for preparation of kilogram quantities of SEX in the purity needed for toxicological studies is being submitted separately.

FOREWORD

Citations of trade names in this report does not constitute an official endorsement or approval of the use of such items.

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GLOSSARY

DADN - 1,5-Diacetyl octahydro-3,7-dinitro-1,3,5,7-tetrazocine
FEP - Fluorinated ethylene-propylene polymer
HMX - 1,3,5,7-Tetranitro-1,3,5,7-tetrazocine
HPLC - High-pressure liquid chromatography
NMR - Nuclear magnetic resonance
RDX - 1,3,5-Trinitro-1,3,5-triazine
SEX - 1-Acetyl octahydro-3,5,7-trinitro-1,3,5,7-tetrazocine
TAT - 1,3,5,7-Tetraacetyl octahydro-1,3,5,7-tetrazocine
TAX - 1-Acetyl hexahydro-3,5-dinitro-1,3,5-triazine
TFAA - Trifluoroacetic anhydride
TRAT - 1,3,5-triacetyl hexahydro-1,3,5-triazine
TLC - Thin layer chromatography

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INTRODUCTION

The U.S. Army Medical Research and Development Command is interested in determining the potential environmental and health hazards of wastewaters containing SEX and TAX. SEX and TAX are unavoidable coproducts formed during the manufacturing of RDX/HMX. In 1977, 34,000 pounds of HMX were produced, or about 123 pounds per day at the Holston Army Ammunition Plant. At full production levels approximately 16 million pounds of RDX and 2 million pounds of HMX can be produced annually, or put another way, more than 1000 pounds of SEX and 3600 pounds of TAX per day could be generated and discharged. The wastewaters from the manufacturing of RDX/HMX are subject to environmental discharge limitations established by regulatory agencies. Information on major constituents of these wastewaters is a necessary portion of the data base needed to estimate the overall environmental hazards. Because the wastewaters will contain large amounts of both SEX and TAX, it is important to obtain sufficient quantities of pure SEX and TAX for a complete toxicological investigation.

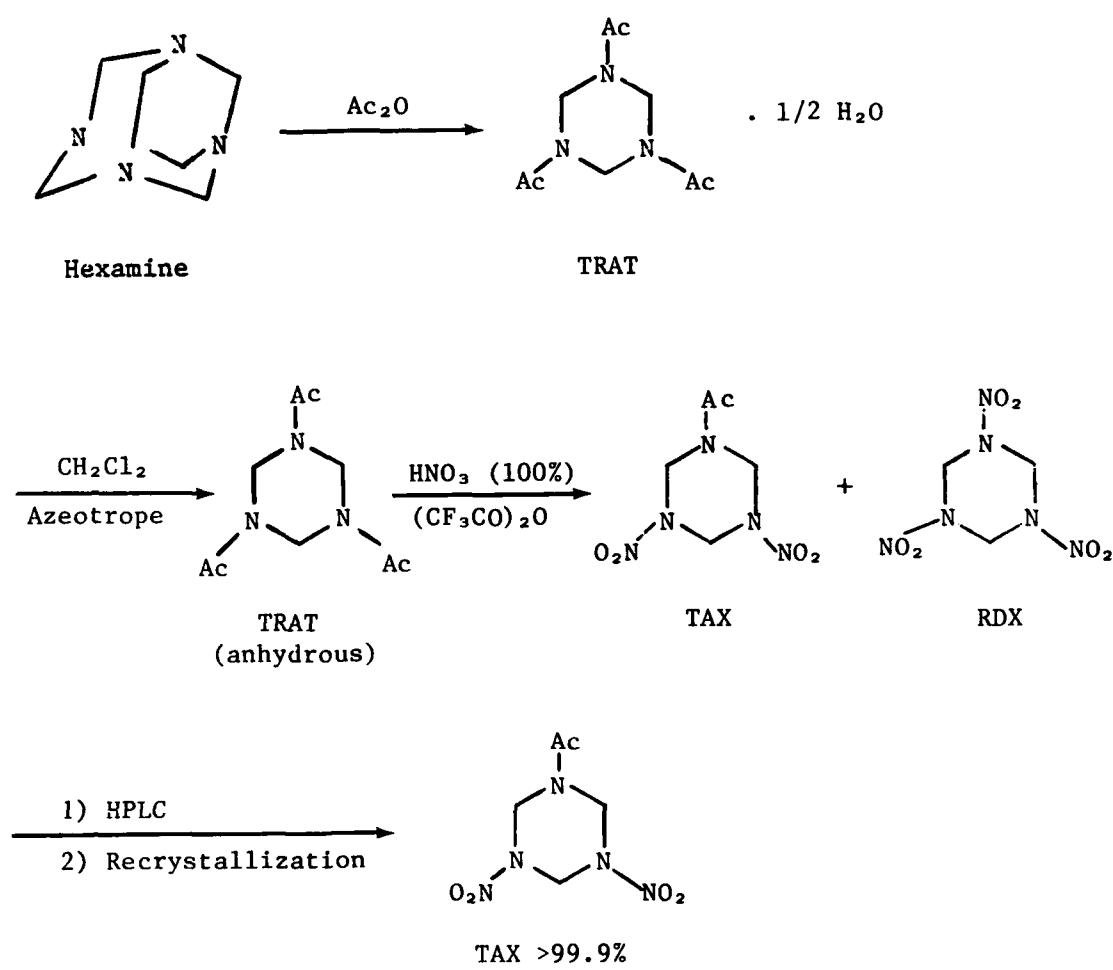
Since SEX and TAX have not been shown to be of value as explosives, little effort has been expended on their deliberate synthesis. Owing to the present toxicological interest, however, it was necessary to explore the feasibility of preparing kilogram quantities of SEX and TAX in the purity (>98%) necessary for these studies. Our specific objectives were:

- (1) Prepare and purify 3 kg of TAX, based on earlier investigations.¹
- (2) Investigate the most promising methods reported for the preparation of SEX and verify successful synthesis of this compound on a 500-gram batch scale.
- (3) Investigate both known and alternative purification methods for SEX to determine which is the most effective.
- (4) Determine the most efficient methodology for the analysis of SEX.
- (5) Prepare a final report fully documenting the information obtained from the study and include a best-efforts cost estimate for the production of the required quantity of SEX.

Our efforts to prepare and characterize SEX are described in the following sections, as is the preparation and purification of an analytically pure 3-kg quantity of TAX. The preparation and purification of TAX and an alternative, but more costly, synthesis of SEX are described elsewhere.^{1,2}

PREPARATION OF TAX

The total synthesis and purification of TAX, prepared according to the method described by Gilbert et al.³ is shown in Scheme I.



Scheme I
Synthesis and Purification of TAX

Preparation of TRAT

TRAT was prepared as previously described.⁴ The TRAT obtained by evaporation of acetic acid/water as a white crystalline solid (melting point 49°-54°C) contained approximately 20% to 30% water (as determined by Karl-Fisher and NMR analysis). The water had to be removed before the TRAT could be mixed with the TFAA. Two methods were developed for removing residual water: (1) drying TRAT in vacuum ovens over phosphorus pentoxide and (2) azeotroping the water with methylene chloride. The methylene chloride azeotroping method was more effective because larger quantities of wet TRAT could be dried. Both methods yielded TRAT containing less than 0.2% water (as determined by Karl-Fisher analysis). The residual water was consumed when TRAT was mixed with TFAA before the TAX production runs were performed. Dried TRAT, obtained by either method, had a melting point of 91°-94°C, identical to that previously reported.⁴

Kilogram Production of TAX

On a laboratory scale, the preparation of TAX by the procedure shown in Scheme I consistently yielded 60% to 70% crude TAX, contaminated with RDX. The experimental methods developed required that the reaction mixture be cooled during admixture of reagents. Subsequently, after a brief induction period and without external cooling, an excursion to an internal temperature of 60°C, accompanied by an uncontrolled refluxing of TFAA, was observed in small-scale synthesis. On scale-up, effective cooling of the reaction mixture in conventional batch equipment was difficult because of the change in the ratio of the volume of material to the effective surface area used for cooling. Furthermore, two unexplained detonations during the initial laboratory experiments precluded scale-up with conventional batch equipment because of the increased hazards involved.

These problems were solved by using a continuous plug-flow method to prepare TAX. The major advantage of the method is the ease of controlling the exothermic reaction. Furthermore, the initial mixing chamber contains only a small amount of material at any one time, increasing the safety of the reaction.

A schematic diagram of the reactor for the TAX synthesis is shown in Figure 1. Approximately 8.3 kg of TRAT was fed into the reactor during a three-day period. Approximately 4.0 kg of a dry TAX/RDX mixture was recovered, which according to the NMR analysis consisted of 75% TAX and 25% RDX. The following optimum conditions were established during this three-day TAX production run.

- A single peristaltic pump cycled cold acetone (10° to 20°F) at a rate of 1.5 L/min through the mixer and separator, coupled in series.
- Feed lines and cooler lines were insulated to minimize heat losses.
- TRAT feed batches were prepared by dissolving 576 grams of anhydrous TRAT in 2 L of TFAA.
- TRAT/TFAA feed rates averaged 60.2 g/min.
- Nitric acid (100%) feed rates averaged 18.0 g/min.
- The above feed rates resulted in a residence reaction time of 15 to 18 minutes.
- The pumps installed below both separator and mixer were operated remotely, keeping the liquid level in both chambers at a volume of 300 to 500 mL.
- During the course of the reaction, four temperatures were monitored: (1) the mixer temperature was held at 66° to 70°F with a cooling bath temperature of 20°F and with the feed rates previously established. (2) The separator temperature remained between 55° and 65°F under these reaction conditions. (3) A coil bath temperature of 65° to 70°F was required to reduce effluent reaction temperatures, which during early runs rose to 125°F. Under the above conditions the effluent temperature remained between 75° and 85°F.

The TAX preparation was interrupted after the separator pump began leaking severely, forcing a complete shutdown of the operation. It was apparent from this run that additional TAX preparations should incorporate the following mechanical modifications:

- (1) A cooler with more efficient and/or larger capacity should be used.
- (2) Mixer and separator flasks should be insulated, and separate pumps should be used to deliver the cooling liquid to provide independent control.

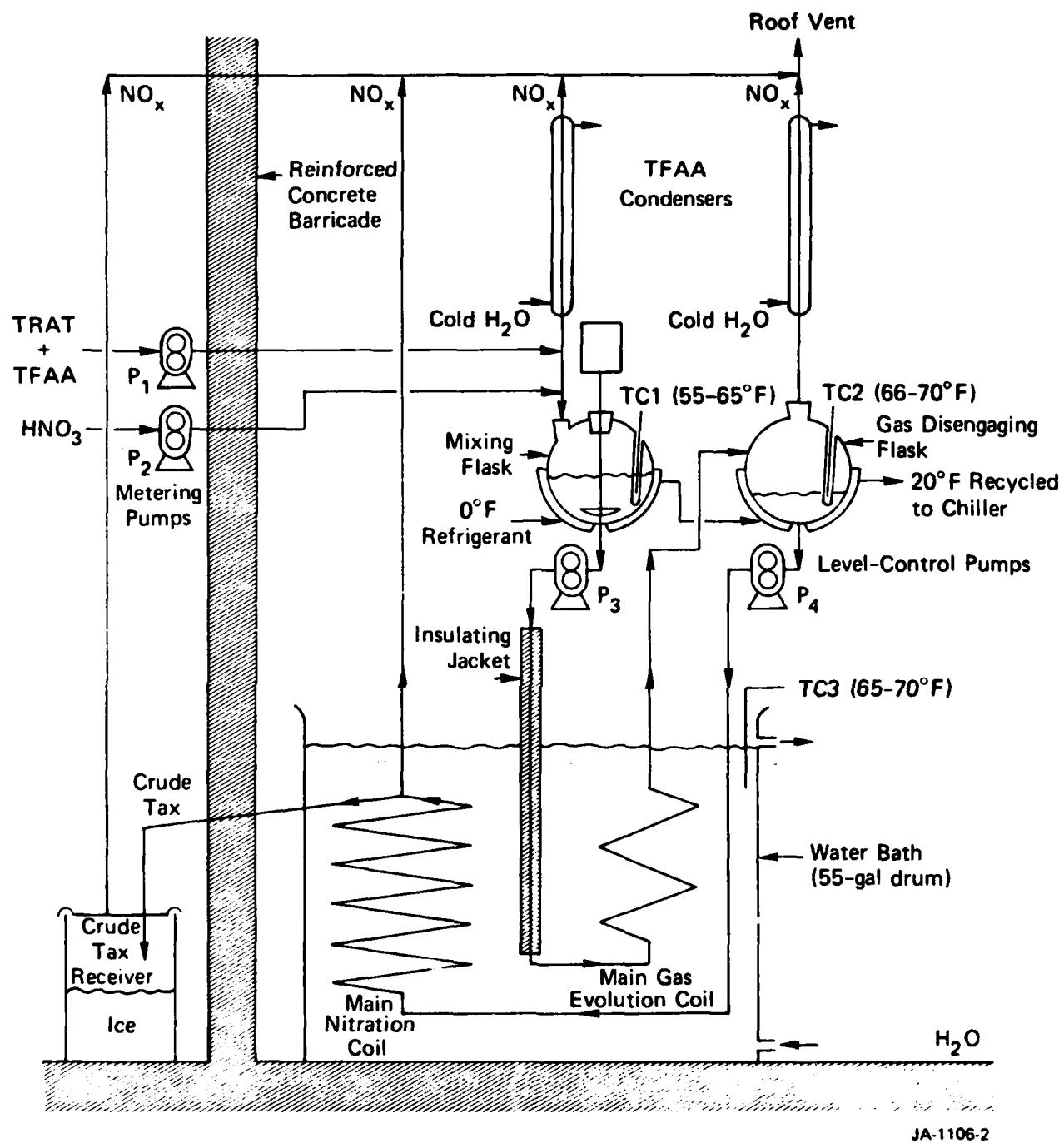
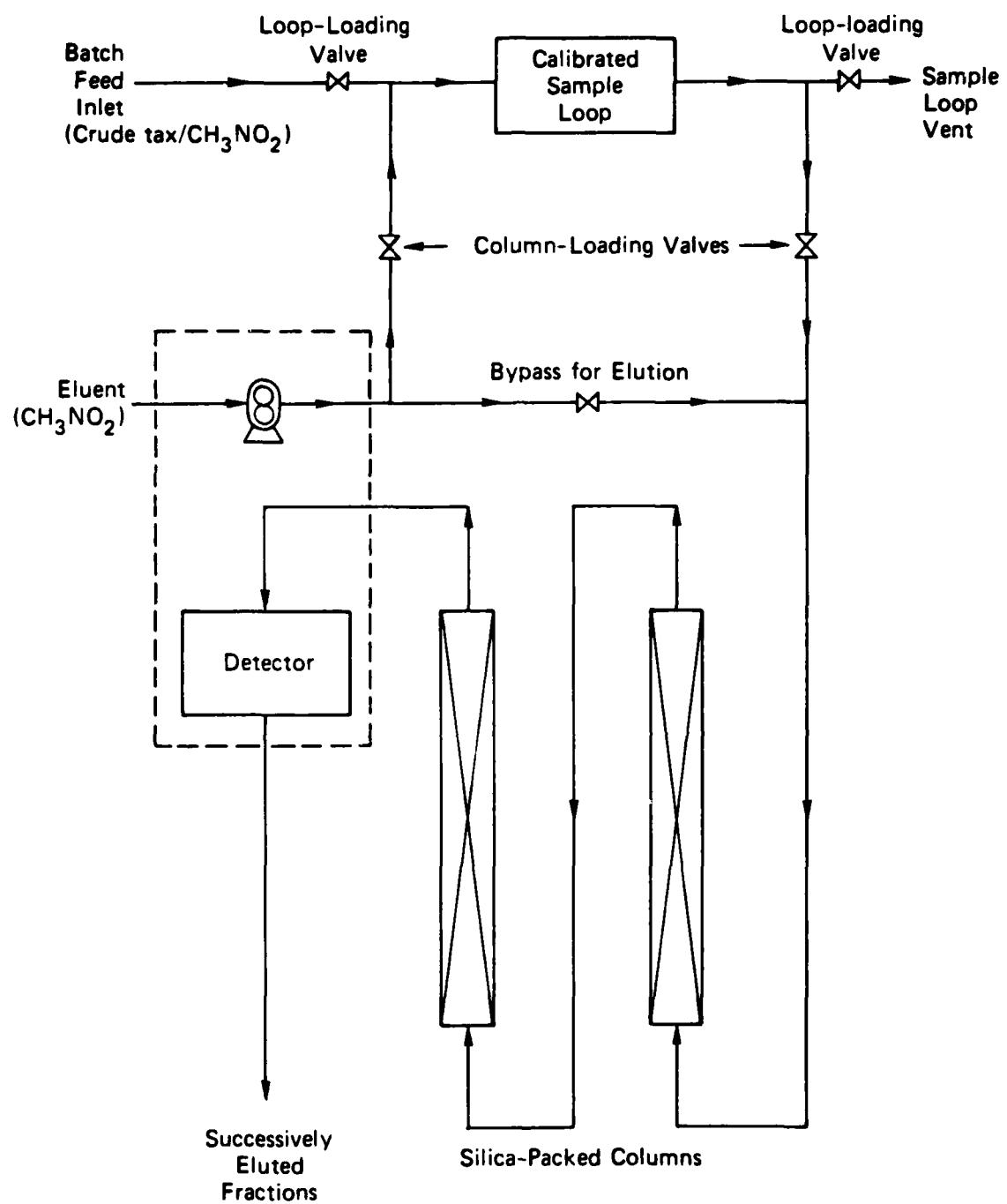


FIGURE 1 SCHEMATIC OF IMPROVED CONTINUOUS-FLOW MINIPLANT FOR MULTIKILOGRAM SYNTHESIS OF TAX

- (3) The pump below the mixer should be controlled remotely and calibrated to match the total feed rates of nitric acid and the TRAT/TFAA mixture.
- (4) Since TAX and/or RDX begin to crystallize during the reaction, the pumps on both the downcomers should be capable of pumping a slurry.

Purification of TAX

The TAX prepared as described above was purified by preparative HPLC, using dual normal-phase prepacked silica gel columns and a nitromethane eluent. Because of the limited solubility of TAX and RDX (approximately 10 g/100 mL) in the solvent, the injection volume must be maximized to ensure a reasonable time frame for purification. A sample loop with a maximum volume of 300 mL was constructed (Figure 2) and attached directly to the columns, bypassing the injector. Evaporation of the nitromethane solution yielded 2.6 kg of light yellow TAX. The color was due to residual impurities in the nitromethane. Recrystallization from a minimal amount of fresh nitromethane yielded 2.3 kg of 99.9% TAX as a white crystalline powder. No impurities could be detected using either normal-phase or reverse-phase analytical HPLC. The process, described above, represents an economic solution to the preparation and purification of multigram quantities of TAX.

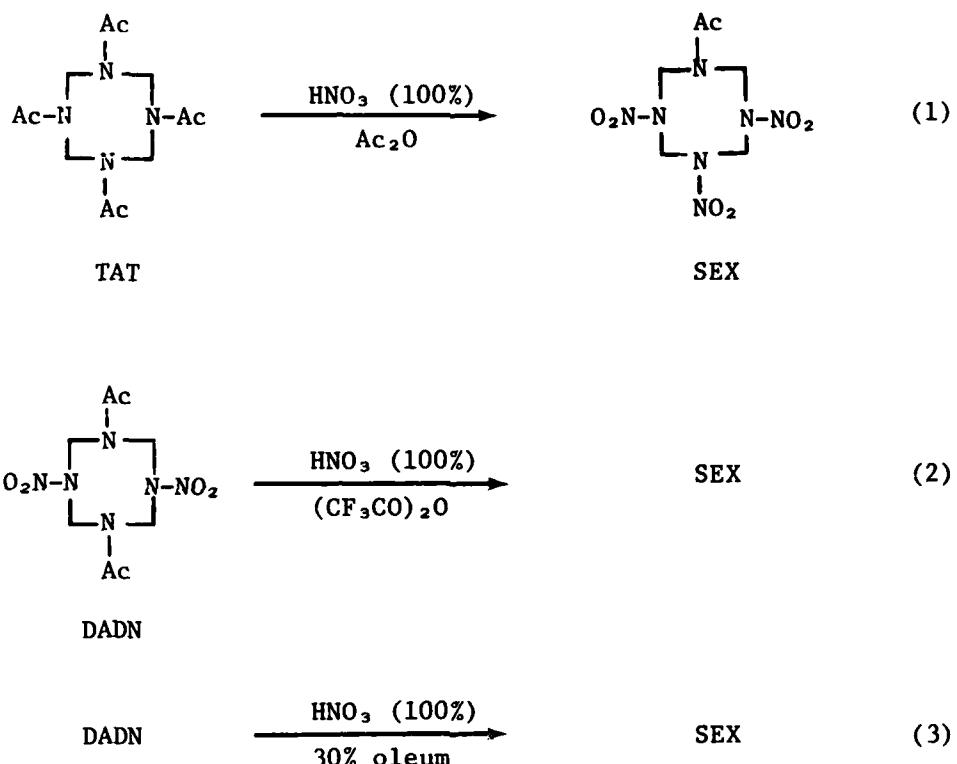


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FIGURE 2 PURIFICATION OF TAX BY PREPARATIVE-SCALE HPLC

PREPARATION OF SEX

SEX was prepared according to the methods of Gilbert et al.⁵ and Coon⁶ as shown in equations (1) through (3).



Treatment of 2.0 grams (7 mmole) of TAT with 100% nitric acid/acetic anhydride mixture yielded 93% and 40% of crude SEX in separate experiments. Based on proton NMR and TLC analysis, the crude SEX was a mixture of DADN, SEX, and HMX in a ratio of approximately 0.5:1:1. The variable yield, coupled with difficult methods for preparing TAT and separating the SEX from contaminants, made this route, shown in equation (1), inadequate for large-scale preparation.

SEX was then prepared from DADN as shown in equation (2). Treatment of up to 40 grams (0.2 mole) of DADN with 100% nitric acid/trifluoroacetic anhydride mixtures consistently yielded 60% to 75% crude SEX. The reaction between DADN and the nitrolyzing medium, 100% HNO_3 /TFAA, was modified slightly from that followed in the preparation of TAX. The DADN was insoluble in TFAA and had to be dissolved in the nitric acid before mixing. Furthermore, when the DADN and the nitrolyzing medium were allowed to stand at room temperature for prolonged periods, no exotherm was observed, such as occurred during the preparation of TAX.

The synthesis, although successful, had two serious drawbacks: (1) the amount of TFAA used in the reaction procedure represented a substantial cost, making the preparation of kilogram quantities of SEX prohibitively expensive, and (2) the crude SEX was contaminated with both HMX and DADN in amounts greater than 50%, which could not be readily removed by physical separation methods, such as column chromatography, recrystallization, or extraction.

Recently, Coon⁶ demonstrated that nitrolysis of DADN with 100% nitric acid/30% oleum as shown in equation (3) yielded a DADN/SEX/HMX mixture consisting of less than 3% HMX. Treatment of up to 500 grams (2.5 moles) of DADN with 100% nitric acid/30% oleum mixtures consistently yielded DADN/SEX/HMX mixtures containing up to 85% SEX, as listed in Tables 1-3. In a typical reaction, 50 grams (0.25 mole) of DADN was treated with 750 mL of 100% nitric acid and 165 mL of 30% oleum. After the mixture was stirred for 18 hours at room temperature, quenched over ice, filtered and dried, 24.4 grams (50% yield) of crude SEX was obtained. The crude material consisted of 3.4% HMX/75% SEX/21.5% DADN (as determined by analytical HPLC), which is equal to a 36.6% overall yield of SEX. This preparation method is superior to those methods previously investigated because (1) the costly TFAA employed in equation (2) is replaced by the more economic and accessible 30% oleum; (2) the reaction can be run at a lower temperature, avoiding hazardous reaction conditions; and (3) the crude SEX obtained is contaminated with smaller quantities of DADN and HMX, making subsequent purification easier.

Reaction Conditions

Before the optimum reaction conditions for SEX preparation could be established, a rapid and accurate method for analyzing DADN/SEX/HMX mixtures had to be developed. Previously NMR was used to give a rough estimate of the composition of the three components. However, the NMR peaks of the compounds overlapped to such a degree that $\pm 5\%$ accuracy was the highest level of confidence that could be achieved. We developed another, more accurate analysis method, i.e., reverse-phase analytical HPLC; however, this system was not satisfactory because the components DADN/SEX/HMX were poorly soluble in aqueous systems.

Therefore, we developed an alternative HPLC analysis method using a microporasil column and a solvent mixture of 30% methylene chloride in acetonitrile. In this solvent system, the DADN/SEX/HMX mixtures were readily soluble. Baseline separation of the three components was achieved with this system, allowing rapid and accurate analysis of SEX production runs.

On the basis of the knowledge gained from examining the nitrolysis reactions of DADN with TFAA/100% nitric acid described previously,² we conducted a series of experiments with 100% nitric acid/30% oleum, that could be analyzed using a two-level factorial design (Table 1). The reactions were run using nitric acid at concentrations of 90% and 98%, reaction temperatures of 40° to 50°C, and reaction times of 20 to 40 minutes. Analysis of the data led to two conclusions: (1) the nitric acid concentration is unimportant over the range investigated and (2) there is an interrelationship between reaction time and reaction temperature.

Maximum SEX yields were obtained by either increasing the reaction temperatures and decreasing reaction time or vice-versa. Because ambient reaction temperatures are likely to result in fewer scale-up difficulties, several reactions were run at room temperature for from 18 to 49 hours (Runs 18, 19, 20, and 30 shown in Table 1). Since the yields of SEX were similar to those achieved at high temperatures, further experimentation and large-scale reactions were conducted at room temperature (24°C).

TABLE 1
OPTIMIZATION OF SEX PRODUCTION

Run	Temp. (°C)	Time (min)	HNO ₃ Conc. ^a (%)	DADN, g.	Product Composition ^b			Total Yield (g)	% Yield SEX
					%HMX	%SEX	%DADN		
1	50	30	98	5.0	2.6	60.7	36.7	2.55	36
2	50	60	98	5.0	2.7	78.7	18.7	0.80	13
3	50	90	98	5.0	2.9	83.4	13.6	0.21	3.5
4 ^c	60	20	98	5.0	--	--	--	0.0	0.0
5 ^d	60	20	98	5.0	3.1	81.3	15.6	1.92	31
6	45	20	98	5.0	3.1	29.5	67.5	3.75	22
7	45	40	98	5.0	2.4	44.0	53.6	3.75	33
8	45°	60	98	5.0	3.8	53.3	42.8	2.95	31
9	45	80	98	5.0	4.0	71.6	24.4	2.00	29
10	40	30	98	5.0	1.8	27.7	70.7	4.45	25
11	40	60	98	5.0	2.3	36.9	60.8	4.10	30
12	40	90	98	5.0	4.4	48.9	46.7	3.45	34
13	40	120	98	5.0	4.7	52.5	42.7	3.30	35
14	40	150	98	5.0	4.8	67.2	28.0	2.10	28
15	55	15	98	5.0	3.6	64.0	32.4	2.11	27
16	55	30	98	5.0	--	--	--	0.0	0.0
17	55	45	98	5.0	--	--	--	0.0	0.0
18	24	1440	98	5.0	3.8	72.6	23.7	1.90	28
19	24	2880	98	5.0	1.6	81.8	15.8	0.50	8
20	24	360	98	5.0	1.3	26.3	72.4	4.09	22
21	50	40	98	10.0	2.0	55.5	42.5	6.22	34.5
22	45	20	90	10.0	1.4	19.3	79.3	9.25	17.9
23	45	40	98	10.0	3.0	53.8	43.2	5.76	31.0
24	45	40	90	10.0	2.3	36.3	59.4	8.56	32.8
25	45	20	98	10.0	1.9	19.3	78.8	9.57	18.5
26	50	20	90	10.0	3.2	26.3	70.5	9.30	24.4
27	50	20	98	10.0	2.9	35.0	62.1	8.52	29.8
28	50	40	90	10.0	2.3	66.6	31.1	5.06	33.7
29	47.5	28	94	10.0	1.9	34.0	64.1	8.78	29.9
30	24	1100	98	10.0	1.1	54.9	44.0	6.30	34.6

^aAll reactions used 37.5 mL of HNO₃ and 17.0 mL of 30% oleum.

^bComposition determined by HPLC analysis.

^cUncontrolled exotherm; temperature increased above 80°C for a short time.

^dTemperature controlled below 75°C.

Having established these conditions we investigated three additional parameters: (1) reaction time, (2) nitric acid concentration, and (3) the relative amount of 30% oleum (see Table 2). The optimum reaction time was 18 to 20 hours. Shorter reaction times resulted in higher isolated DADN percentages, whereas longer reaction times reduced overall SEX yields. The net yield of SEX using 98% nitric acid was higher than that obtained with 90% nitric acid; thus 98% nitric acid was selected for further experimentation. Increasing the oleum concentration was expected to reduce the amount of HMX formed in the final product. However, when the oleum concentration was increased, the nitrating power of the system decreased; this had little effect on the HMX content in the final product, but reduced the overall yield and purity. Decreasing the amount of oleum had a less deleterious effect: HMX increased slightly while the DADN decreased. On the basis of these results we selected the conditions shown in Runs 8 and 10 of Table 2 for scale-up reactions.

Using the established reaction conditions, we conducted a series of 50- and 100-gram batch reactions (Table 3). The results were similar to reactions run on a 10-gram scale, and no serious problems occurred with scale-up. Generally, shorter reaction times decreased the SEX content in the final product (see Runs 2 and 3, Table 3). Increasing the reaction time resulted in consistently good overall crude SEX yields, ranging from 40% to 50% material balance with SEX compositions of from 79% to 85%. The discrepancies in yield could be attributed to collection techniques, which were not always consistent.

Because no difficulties were encountered when the reaction was scaled up, a final 500-gram batch reaction was conducted. A mixture of 500 grams of DADN, 3750 mL of 98% nitric acid, and 825 mL of 30% oleum was stirred overnight at ambient temperature. The exothermic addition of the oleum was readily controlled with a dry ice/acetone bath. Workup of the reaction, in the usual manner, yielded 158 grams of crude SEX, which was composed of 86% SEX, 4% HMX, and 10% DADN (as determined by analytical HPLC). This correlates to an overall SEX yield of 27%. The slightly lower overall yield coupled with a somewhat higher SEX composition was attributed to an increased reaction time. For

Table 2
DADN NITROLYSIS REACTIONS AT ROOM TEMPERATURE^a

Run	Time (hr)	HNO ₃ ^b Conc. (%)	30% Oleum, g/g DADN	Composition ^c			Yield (g)	% Yield SEX
1	6	98	6.4	1.3	26.3	72.4	8.18	22.0
2	24	98	6.4	3.8	72.6	27.7	3.80	28.0
3	48	98	6.4	1.6	81.8	15.8	1.00	8.0
4	18	98	6.4	1.1	54.9	44.0	6.30	34.6
5	21	98	6.4	3.7	81.7	14.7	2.39	19.5
6	21	90	6.4	2.3	79.5	18.2	2.00	15.9
7	18	90	6.4	1.8	71.3	26.9	3.79	27.0
8	18	98	3.2	4.3	81.5	14.2	3.97	32.4
9	18	98	9.6	2.2	35.2	62.7	7.82	27.5
10	18	98	3.2	4.8	81.2	14.0	3.75	30.5
11	18	90	3.2	6.6	76.7	16.7	3.70	28.4

^aAll reactions based on a 10-g scale of DADN.

^bAll reactions used 75.0 mL of HNO₃ at the concentration indicated.

^cComposition determined by analytical HPLC.

Table 3
DADN NITROLYSIS: 50- AND 100-g BATCH REACTION AT 24-27°C^a

Run	Time (hr)	Yield (g)	Composition ^b			% Yield SEX
			% HMX	% SEX	% DADN	
1	24	16.9	4.2	84.4	11.4	28.6
2	18	24.4	3.4	75.0	21.5	36.6
3	18.5	57.1	2.7	70.5	26.8	40.3
4	19.5	40.2	2.9	85.0	12.1	34.2
5	19.5	42.8	3.0	81.7	15.3	34.9
6	19.5	50.4	2.0	79.5	18.5	40.1
7	19.5	45.2	1.8	84.0	14.2	38.0

^aThe 20-g batch reactions used 375 mL of 98% nitric acid and 82.5 mL of 30% oleum; 100-g batch reactions used 750 mL of 98% nitric acid and 165 mL of 30% oleum.

^bComposition determined by analytical HPLC.

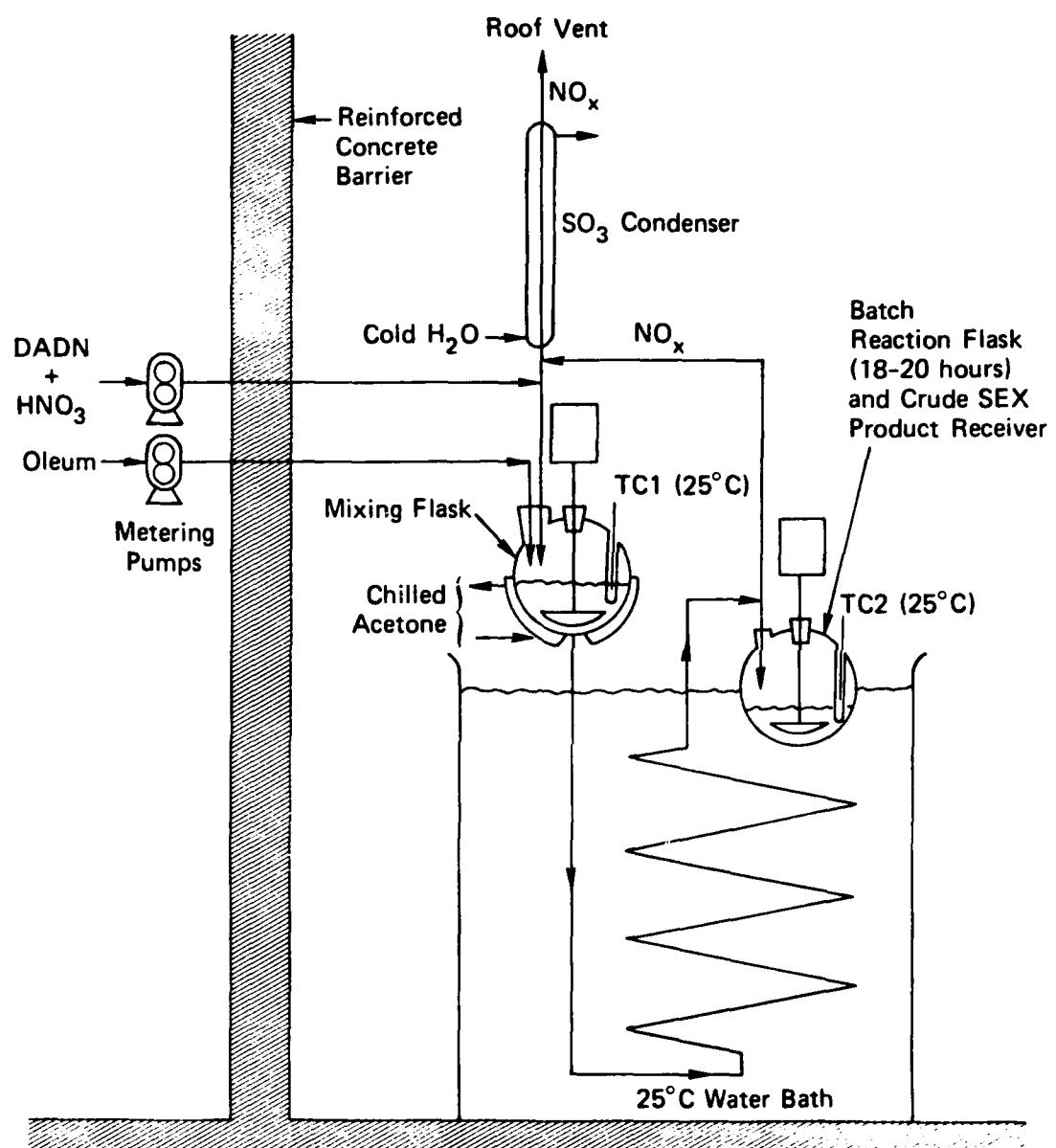
future 500-gram batch reactions, a heat exchanger apparatus, shown in Figure 3, will be used for the initial mixing of reagents. This will allow the final reaction temperature to be adjusted to ambient temperature and avoid warm-up times, making the reaction times more consistent.

Thus, experimental conditions developed during this phase of the program will allow for rapid and consistent preparation of moderate-purity SEX (75% to 85%). The expensive TFAA, originally used in the DADN nitrolysis reaction, has been replaced with the more economical and available 30% oleum. The new method allows for the preparation of 75% to 85% SEX in the crude reaction mixtures, contaminated with only 1% to 5% HMX and 10% to 20% DADN. This can be compared with earlier studies using TFAA nitrolysis conditions in which 40% to 50% of the crude reaction mixture proved to be HMX and DADN. Furthermore, using the established reaction conditions, i.e., ambient temperatures for 18 to 20 hours, avoids the potentially hazardous conditions that accompany elevated reaction temperatures.

Purification of SEX

As stated, the crude SEX obtained from the large scale reactions described above contained a maximum of 30% of DADN and HMX, in variable amounts (Table 3). Our previous work² showed that extraction, crystallization, and complexation were ineffective purification procedures. However, effective purification was achieved by successive chromatographic separations. The first, hot-column chromatography, removed all traces of DADN. The second, preparative HPLC, separated SEX and HMX, yielding 99+% SEX. The major drawback of this purification procedure is the second step. Because of the low solubility of SEX/HMX mixtures in nitromethane (approximately 3 g/100 mL of eluent), purification by preparative HPLC would require prohibitively long labor times.

The new synthesis procedure yielded crude DADN/SEX/HMX mixtures containing only 1% to 5% HMX. These high-purity SEX mixtures (75% to 85% SEX) could be purified to greater than 95% SEX by hot-column chromatography, which removed the majority of the DADN and a portion of the HMX. The resulting 95% SEX was further purified to greater



JA-1106-4

FIGURE 3 SETUP FOR SCALE-UP OF SEX SYNTHESIS

than 98+% SEX by recrystallization from acetone. Although substantial amounts of SEX remain in the acetone recrystallization solvent system (approximately 50% recovery of 98+% SEX by this method), this effort has culminated in an effective and economic purification procedure, yielding SEX of adequate purity for subsequent toxicological testing. Even though a successful method has been developed for the preparation and purification of kilogram quantities of SEX, we recommend procurement of only 95+% SEX because 98+% SEX requires approximately twice the effort and a substantial increase in cost.

Hot-Column Chromatography

SEX/HMX mixtures have been purified by preparative HPLC on silica gel using a nitromethane eluent.² Moreover, adequate separation of DADN, SEX, and HMX was obtained on TLC plates using a variety of polar eluents such as nitromethane, acetonitrile, and acetone; however, column chromatographic separation was hampered by the low solubility of the crude SEX mixtures. For example, the solubility of crude DADN/SEX/HMX mixtures in refluxing nitromethane is approximately 5 g/100 mL and in acetone only 1 g/100 mL. At ambient temperatures the solubility in both solvents was halved. To maximize the solubility of crude SEX mixtures and overcome potential precipitation of materials from solution during chromatography, we attempted to separate the DADN/SEX/HMX mixtures by hot-column chromatography. Table 4 shows the results of several hot-column chromatographic trials. The column temperature was maintained between 90° and 100°C by running steam through the system. Nitromethane was selected as the eluent solvent because (1) its boiling point, 103°C, is high enough to avoid excessive internal boiling and (2) the solubility of the crude DADN/SEX/HMX mixtures was highest in nitromethane, as stated above. Thus, a 50-g sample of crude SEX (composed of 10.0% DADN, 86.0% SEX, and 4.0% HMX) was purified using a 3-inch-diameter, 4-foot-long, jacketed column, packed with 5 pounds of 90-200 mesh silica gel, yielding 95+% SEX essentially free of DADN, Table 4. Furthermore, because the pressure can be adjusted to control both the flow rate and internal refluxing of the nitromethane. It was also possible to obtain partial separation of small amounts of HMX contamination during this stage of purification. Essentially, the apparatus shown in Figure 4 is a low pressure, hot-column liquid chromatograph. The elevated temperature makes purification of kilogram quantities of SEX economically more feasible than operation at lower temperatures.

Table 4
HPLC-COLUMN CHROMATOGRAPHY OF HMX/SEX/DADN^a

Run	Amount (μ g)	Composition of Starting Material ^b			Composition ^b Recovered Material			Amount Recovered (g)	% SEX Recovered	Time (hr)	Flow rate (ml./min.)
		% DADN	% SEX	% HMX	% DADN	% SEX	% HMX				
1	22.1	14.4	81.9	3.7	0.3	95.6	4.1	13.70	75.6	1.2	1
2	5.0	42.5	55.5	2.0	1.4	94.0	4.6	1.12	40.4	0.25	100
3	5.0	21.8	74.0	4.2	0.5	93.2	6.2	3.18	85.9	0.25	50
4	5.0	14.1	78.7	4.2	0.8	94.1	5.0	3.50	88.9	0.5	25
5	20.0	21.5	75.0	3.4	0.1	95.8	4.1	12.77	85.1	3	20
6	25.0	26.8	70.5	2.7	0.4	93.6	5.9	12.70	67.8	3	20
7	25.0	26.8	70.5	2.7	0.8	96.1	3.1	17.70	96.5	2	20
8	19.9	19.3	77.1	3.6	1.2	95.6	3.2	12.9	80.4	2	20
9	50.0	10.0	86.0	4.0	1.5	96.0	2.5	35.0 ^c	78.6 ^d	4	40
10	50.0	10.0	86.0	4.0	0.3	95.9	3.8	38.8	86.5	4	40
11	55.5	10.0	86.0	4.0	0.4	95.8	3.8	45.6	91.5	4	40

^aNitromethane used as eluent, 100°C temperature.

^bComposition determined by analytical HPLC.

^cAn additional 10.0 g of 8.1% HMX, 91.9% SEX was recovered from the column.

^dIncluding other fractions, total of 99% SEX recovered.

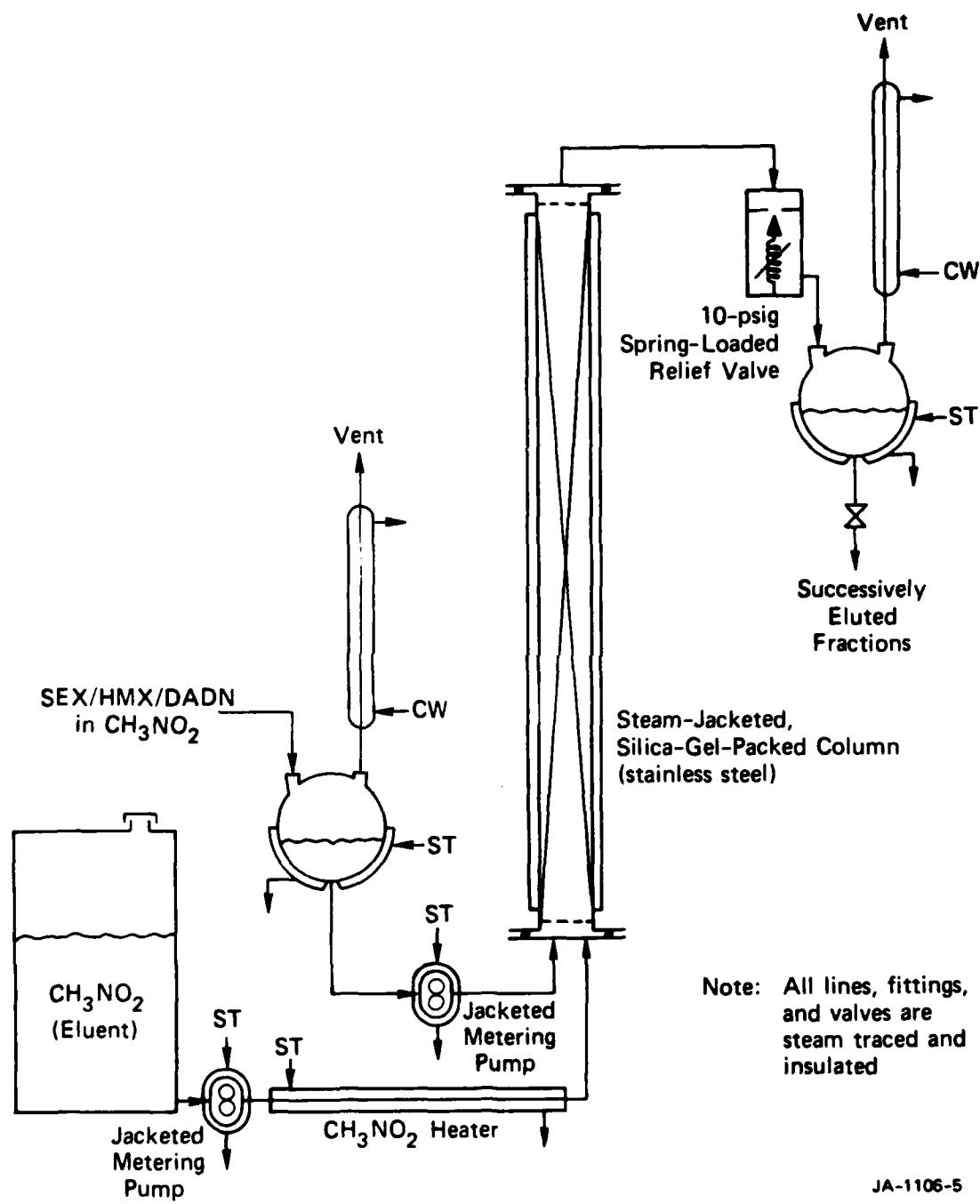


FIGURE 4 PURIFICATION OF SEX BY LOW-PRESSURE HOT-COLUMN LIQUID CHROMATOGRAPHY

Crystallization

Recrystallization was first attempted on crude DADN/SEX/HMX mixtures.² The DADN rapidly precipitated from all solvent systems examined and afforded nucleation sites for both SEX and HMX. The precipitation accounts for observed low purity of SEX in samples containing significant quantities of DADN. However, the products obtained from the hot-column separations described above contained little DADN (generally less than 1.0%). Thus, recrystallization was an effective method for separating the remaining 4% to 5% HMX, yielding greater than 98+% SEX. Also, the effectiveness of the recrystallization may have been enhanced by the fact that HMX is more soluble than SEX in most solvents and is present in such small amounts. Acetone appears to have been the most effective solvent for recrystallization (Table 5), yielding products whose composition was consistently greater than 98% SEX. Large amounts of acetone were required (approximately 100 mL/g) and crystallization was slow, taking several days. The slow rate of crystallization seems to have helped prevent cocrystallization of HMX, and the purity increased with successive batches of crystals recovered over time. With this purification method, i.e., hot-column chromatography on silica gel using a nitromethane eluent, followed by slow recrystallization from acetone, 98+% SEX could be obtained.

Table 5
RECRYSTALLIZATION OF SEX/HMX MIXTURES

Solvent (mL)	Amount ^a Dissolved (g)	Amount ^b Recovered (g)	Composition ^c		
			% HMX	% SEX	% DADN
Nitromethane (30)	1.0	0.70	2.0	97.9	0.1
Acetonitrile (25)	1.0	0.85	1.4	98.6	0.0
Cyclohexanone (30)	1.0	0.70	1.2	98.6	0.1
Cyclohexanone (20)	1.0	0.80	1.3	98.2	0.4
Dimethylsulfoxide: water (10:4)	1.0	0.68	3.6	95.9	0.5
Dimethylsulfoxide: water (8.2:4)	1.0	0.63	4.0	95.5	0.5
Dimethylsulfoxide: water (5:2)	1.0	0.61	3.6	95.9	0.5
Dimethylsulfoxide: water (5:1)	1.0	0.43	2.3	97.0	0.7
Acetonitrile (25)	1.0	0.63	3.3	96.3	0.3
Acetone (25) ^d	1.0	0.55	2.4	97.6	0.0
Acetone (100)	1.0	0.52	0.8	98.6	0.6
Acetone (300)	2.7	1.47	0.8	98.6	0.6
Acetone ^e (800)	7.4	4.06	0.3	99.6	0.1
Acetone ^f (1700)	16.4	9.35	0.7	98.5	0.8
Acetone ^g (1700)	17.6	8.2	1.5	98.0	0.5
Acetone ^h (1200)	12.9	6.5	1.4	97.9	0.6

^aInitial composition 93.6% SEX, 5.9% HMX, 0.4% DADN.

^bTotal amount recovered over 5-day period.

^cComposition determined by analytical HPLC.

^dConcentrated down from 100 mL.

^eInitial composition 95% SEX, 4.7% HMX, 0.3% DADN.

^fInitial composition 96.0% SEX, 3.2% HMX, 0.7% DADN.

^gInitial composition 96.1% SEX, 3.1% HMX, 0.8% DADN.

^hInitial composition 95.6% SEX, 3.2% HMX, 1.2% DADN.

CONCLUSIONS

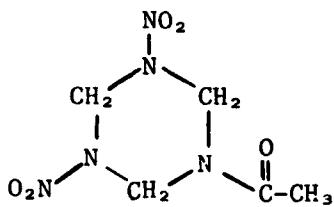
TAX was prepared in kilogram quantities by use of a continuous plug-flow method. The major advantages of the method were the ease of controlling the reaction exotherm and the minimizing of the potentially hazardous reaction conditions that had resulted in two unexplained detonations during initial experiments.

An effective and comparatively economical method for preparing and purifying SEX has been developed. Nitrolysis of DADN with 100% nitric acid/30% oleum mixture consistently yields 75% to 85% pure SEX, contaminated with from 2% to 5% HMX and 10% to 20% DADN. This material can be purified to 98% SEX by hot-column chromatography with a nitromethane eluent, followed by recrystallization from acetone. Although this method is successful, we recommend that 95% SEX be procured because recrystallization from acetone results in a 40% to 50% material loss. This loss, which occurs in the final step of the procedure, results in twice the overall effort for only a 3% increase in purity.

CHARACTERIZATION OF TAX

TAX appears sufficiently stable in normal nitrolysis media to exist as a contaminant in RDX/HMX manufacturing process. The characteristics of TAX are as follows:

Structural Formula:



Empirical Formula: C₅H₉N₅O₅

Elemental Analysis: Calculated: C, 27.39; H, 4.11; N, 31.96

Found: C, 27.45, 27.40; H, 4.14, 4.16; N, 31.75, 31.87

Melting Point: 158°-159°C

Density: 1.675 g/cm³ at 21°C

Molecular Weight: 219 (Calculated)

Solubility: Soluble in acetone, acetonitrile, methanol, ethanol, and nitromethane. Insoluble in trifluoroacetic acid.

Impact Sensitivity (drop weight test): Greater than 300 kg-cm compared with 134 kg-cm for pure RDX. TAX is insensitive to direct strong hammer blows. During our investigations TAX has not exhibited any impact sensitivity.

Infrared spectrum: See Figure 5.

Proton NMR Spectrum: See Figure 6.

Chemical Properties: TAX is destroyed rapidly by 96% sulfuric acid.

Purity: The purity of TAX was determined by analytical HPLC using a reverse-phase system with 30/70 methanol/water eluent. An internal standard of 1,3,5-trinitrobenzene was used with 1/R_f values of 2.39 for RDX and 3.21 for TAX. Column chromatographed TAX contained no detectable amounts of TRAT (starting material) or RDX (major contaminant of crude reaction mixtures). Also, no other contaminants were detected by HPLC, ensuring a 99.9+% purity of material.

No. 007-1493

PEEKIN-EL-MEEB

CONCENTRATION <u>5 % TAX/ 500 mg KBr</u>	SCAN MODE <input type="checkbox"/> ACCY. <input type="checkbox"/> HI ENERGY <input type="checkbox"/>	SURVEY <input type="checkbox"/>	SPECTRUM NO. <u>IR-111737-66-1</u>
THICKNESS <u> </u>		CAL. <input type="checkbox"/>	SAMPLE <u>—1-Acetylhexahydro-3,5-dinitro-1,3,5-triazine (TAX)</u>
PHASE <u>KBr Pellet</u>	RESOLUTION <input checked="" type="checkbox"/>		
REMARKS <u>99.9+ % TAX</u>	OPERATOR C.D.B.	DATE <u>4-15-80</u>	ORIGIN Recrystallized from CH ₂ Cl ₂

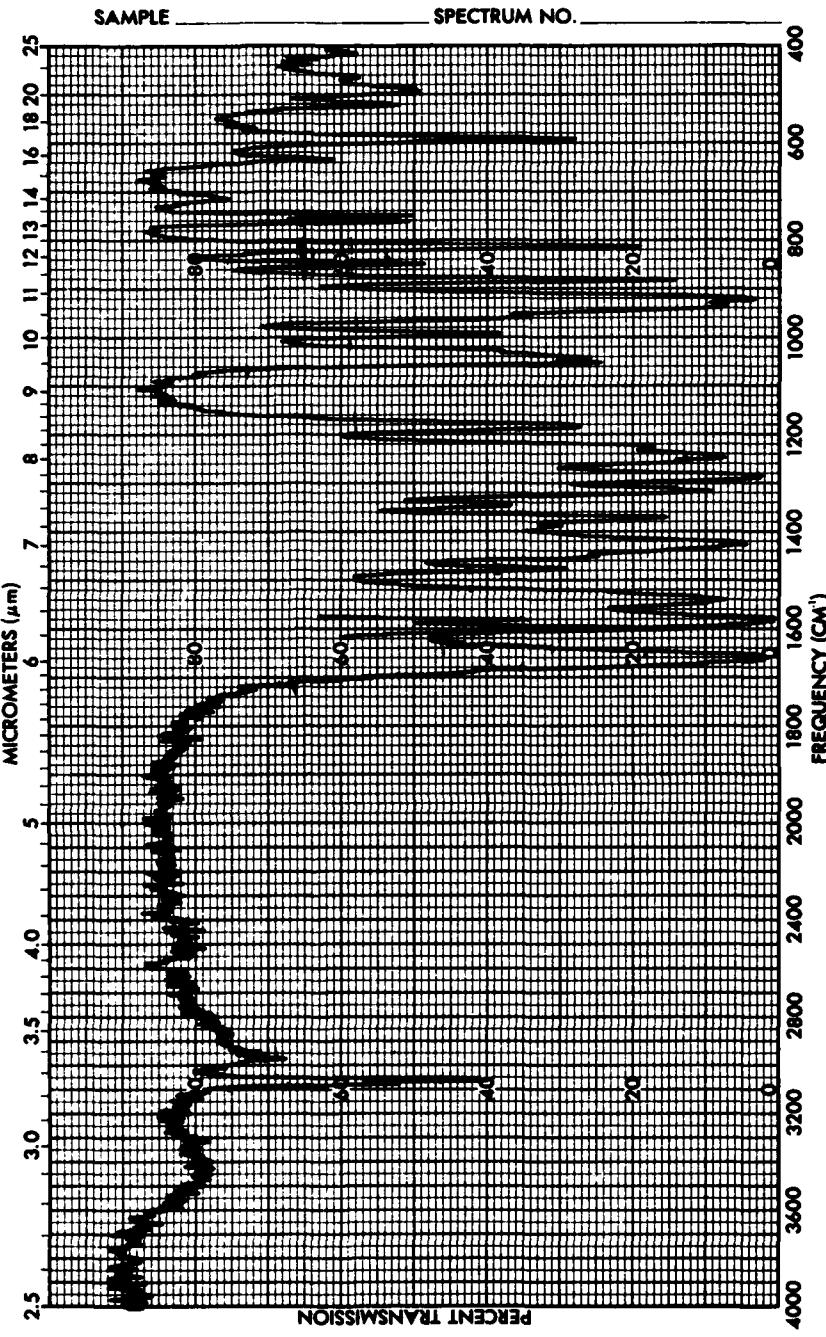


FIGURE 5 INFRARED SPECTRUM OF 99.9% TAX

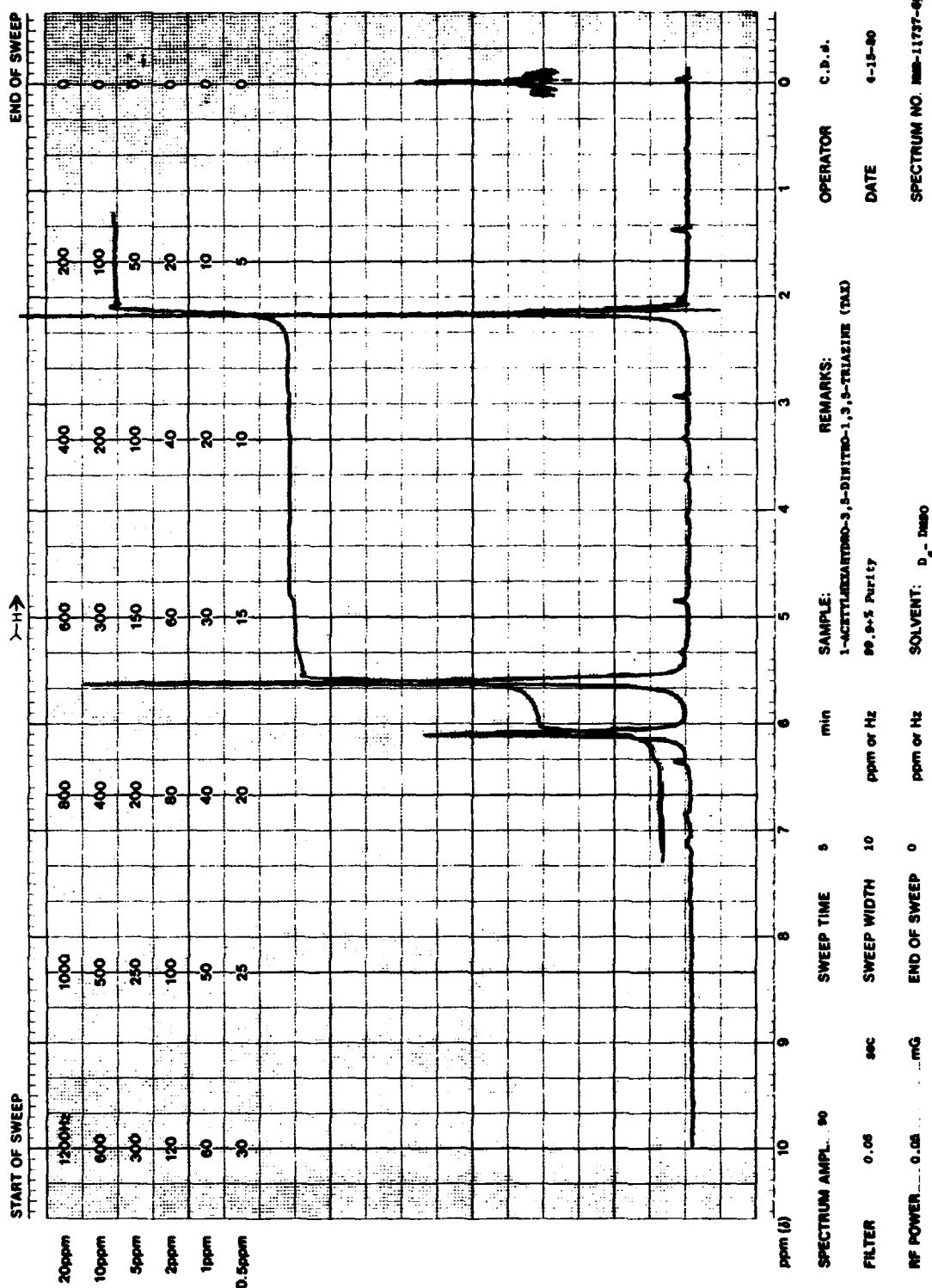
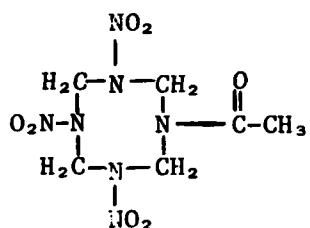


FIGURE 6 NMR SPECTRUM OF 99.9% TAX

CHARACTERIZATION OF SEX

SEX appears sufficiently stable in normal nitrolysis media to exist as a contaminant in RDX/HMX manufacturing process. The characteristics of SEX are as follows:

Structural Formula:



Empirical Formula: $\text{C}_6\text{H}_{11}\text{N}_7\text{O}_7$

Elemental Analysis: Calculated: C, 24.57; H, 3.75; N, 33.45
C, 24.21; H, 3.76; N, 33.45

Melting Point: 237°-237.5°C (DEC)

Density: 1.785 g/cm³ at 21°C

Molecular Weight: 293 (Calculated)

Solubility: Soluble in dimethylsulfoxide. Slightly soluble in acetone, nitromethane, and acetonitrile. Almost insoluble in ethanol, benzene, and ether.

Impact Sensitivity (drop weight test): Greater than 300 kg-cm compared with 148 kg-cm for pure HMX. SEX is sensitive to direct strong hammer blows. During our investigations SEX has exhibited no instability, but because of the hammer results should be handled as a potential explosive, like HMX.

Infrared Spectrum: See Figure 7.

Proton NMR Spectrum: See Figure 8.

Chemical Properties: SEX gives a positive Franchimont nitramine reaction, but a negative Liebermann nitroso test. Decomposition in hydroxide fails to produce free CH_3COO^- for a lanthanum nitrate test.

NO. 007-1493

PERKIN-ELMER

CONCENTRATION 5 mg SEX/ 500 mg KBr	SCAN MODE	ACCY. <input type="checkbox"/>	SURVEY <input type="checkbox"/>	SPECTRUM NO. IR-11784-10-1
THICKNESS	HI ENERGY <input type="checkbox"/>	CAL. <input type="checkbox"/>	SAMPLE	1-Acetyl octahydro-3,5,7-trinitro
PHASE KBr Pellet	RESOLUTION <input checked="" type="checkbox"/>			1,3,5,7-tetrazocine (SEX)
REMARKS 99.9% SEX	OPERATOR C.D.B.	DATE 9-16-80	ORIGIN Recrystallized from CH ₂ NO ₂	

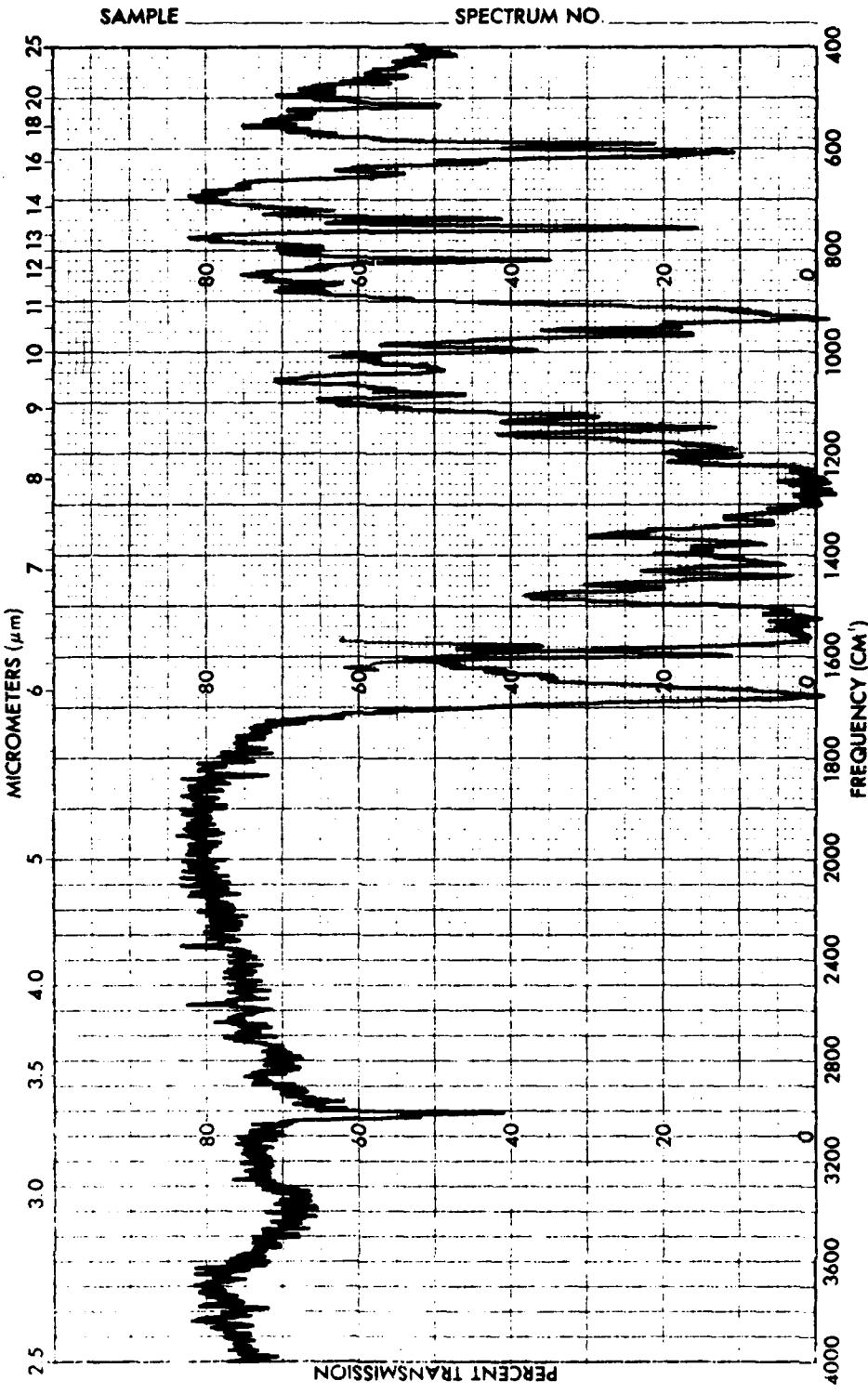


FIGURE 7 INFRARED SPECTRUM OF 99.9% SEX

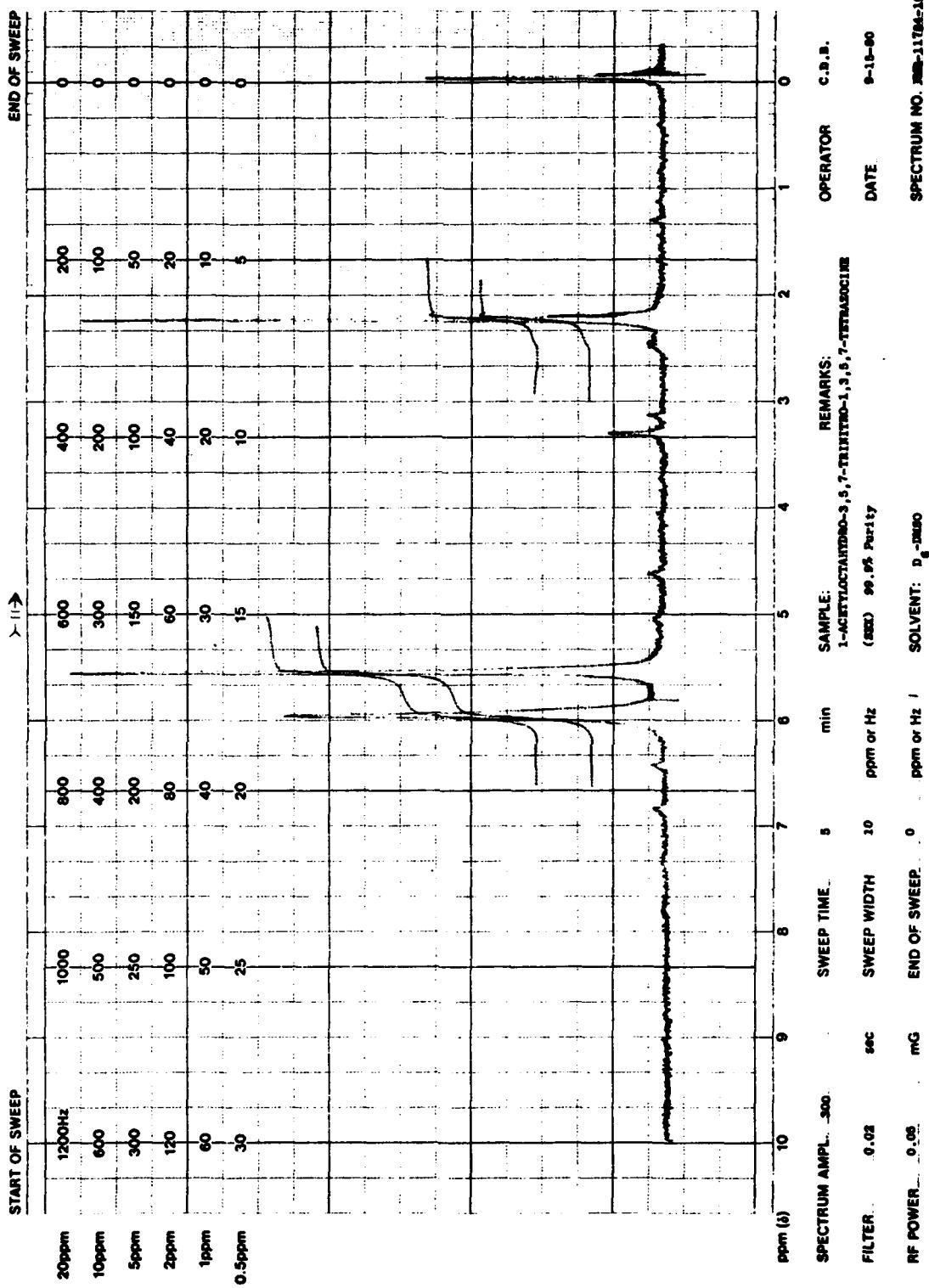


FIGURE 6 PROTON ENERGY SPECTRUM OF 20-30-50-80

However, if SEX is decomposed in 96% sulfuric acid, the distillate gives a lanthanum nitrate test.⁷

SEX appears inert to boiling acetic anhydride and unaffected by treatment with ammonium nitrate-nitric acid mixtures. Absolute nitric acid at 50°-60°C converts SEX to HMX. Warm 70% nitric acid destroys the compound rapidly, as does 10% aqueous sodium hydroxide and 28% ammonia.

Purity: The purity of SEX was determined by analytical HPLC with a Spectra-Physics 3500B Liquid Chromatograph. A waters RCM-100, C₁₈ cartridge with a mobile phase of 80/20 water/methanol was used for DADN/SEX/HMX mixtures. An internal standard of RDX was used with $1/R_f^*$ values of 1.5 for HMX, 1.5 for SEX, and 1.7 for DADN. Hot-column chromatographed SEX contained no detectable amounts of DADN (starting material) and only 1% to 2% HMX (sole contaminant). High pressure liquid chromatographed material contained no DADN or HMX. Also, no other contaminants were detected by analytical HPLC, ensuring a 99.9+% purity of SEX.

^{*} R_f = response factor.

EXPERIMENTAL PROCEDURES

1,3,5-Triacetylhexahydro-1,3,5-Triazine (TRAT) ⁴

Hexamine (10 g, 72 mmole) was added at room temperature with stirring to acetic anhydride (41, 0.4 mole). A mild exotherm raised the temperature to 35°C, after which the mixture was heated for 2/hr at 98°C. The solution was cooled to 5°C, 200 mL of water was added, and the mixture was stirred for 30 min. The solution was then reduced to a viscous yellow liquid by vacuum distillation. Water (25 mL) was added, and the mixture was cooled and stirred to induce precipitation. The solid product was filtered and dried in vacuo over sodium hydroxide pellets, yielding 8.6 g (59.7%) of white crystalline TRAT, m.p. 91°-94°C (literature m.p., 93°-96°C). Alternatively the residual water could be removed by azeotroping with methylene chloride. 200-Fold increase in the amount of hexamine (2 kg, 5.6 moles) afforded 1.07 kg (74.7%) of TRAT, m.p. 92°-94°C.

1-Acetylhexahydro-3,5-Dinitro-1,3,5-Triazine (TAX)

As an important caution, we note that during our investigations on the preparation of TAX, two unexplained detonations occurred with no forewarning. Injury to personnel was avoided because adequate safety measures were in force at the time of the explosions.

Batch Preparation of TAX. The following preparative procedure, a modification of that described by Gilbert et al.,⁵ was found to be superior to those described in the literature. TRAT (1.4 g, 7.0 mmole) and trifluoroacetic anhydride (7.6 g, 36.5 mmole) were mixed at 15°C in a flask equipped with a magnetic stirrer, dropping funnel, and external cooling bath. Nitric acid (3.0 g of 100% acid, 48 mmole) was added dropwise with stirring and cooling at 15°-20°C. The cooling bath was

removed, and stirring was continued for 15 min. The solution was then poured into 100 mL of ice water. The white precipitate was filtered and dried in vacuo over P_2O_5 affording 0.95 g (58% yield) of crude TAX. HPLC analysis of the crude TAX indicated a 94% composition of TAX with only 6% RDX as the major contaminant.

Plug-Flow Preparation of TAX. For this preparation, we used a four-necked, 35 mL flask equipped with a mechanical stirrer, thermometer, condenser, two inlet tubes, and an overflow outlet located approximately 1.2 in. from the bottom of the flask. The apparatus was cooled in an ice/water bath, during which time 27 g of TRAT (0.12 mole) dissolved in 144 g of trifluoroacetic anhydride was added at a rate of 1 mL/min by using a constant addition syringe. Simultaneously, 100% HNO_3 was introduced through the other inlet at a rate of 0.33 mL/min. The resulting mixture was stirred vigorously and constantly overflowed into a 3.6-ft length of 1/4-in.-O.D. glass and FEP tubing immersed in water. The total volumetric feed rate of approximately 1.33 mL/min corresponded to a nominal reaction residence time of 15 min in the FEP tubing, neglecting gas evolution. The discharge from the FEP tubing was immediately quenched into a ice/water bath, precipitating the crude TAX. This material was then filtered, washed with several small portions of ice water, and dried in vacuo over P_2O_5 , affording 17.1 g (63%) TAX.

The material composition of the crude TAX as determined by analytical HPLC was 90% TAX, 6.4% RDX, and 3.4% TRAT.

Purification of TAX by Open Column Chromatography. A column packed with 400 g of 90-200 mesh silica gel was charged with 8.4 g of crude TAX dissolved in 35 mL of a 1:1 mixture of nitromethane:dichloromethane. The column was eluted with the same solvent mixture, and each fraction (75-mL portions) was examined by TLC. Fractions containing like components were combined and concentrated. The first 500 mL of effluent yielded 1.9 g of RDX upon concentration. After approximately 100 mL of solvent containing no material, the major component, 6.41 g of TAX (essentially quantitative recovery of material), eluted with the next

600 mL of solvent. Analytical HPLC showed this material to be greater than 99.9% TAX.

Elemental analysis: Calculated for $C_5H_9N_5O_5$: C, 27.39; H, 4.11; N, 31.96. Found: C, 27.45, 27.40; H, 4.14, 4.16; N, 31.75, 31.87.

1-Acetyl octahydro-3,5,7-Trinitro-1,3,5,7-Tetrazocine (SEX): TFAA Nitrolysis

DADN (7.5 g, 26 mmole) was dissolved in 50 mL of 100% HNO_3 at 20°C. With cooling (ice/water bath), 7 mL of trifluoroacetic anhydride was added dropwise such that the temperature of the mixture remained between 15° and 20°C. At the end of addition, the flask was placed in a water bath preheated to 35°C and stirred for 80 min at this temperature. The mixture was then poured into ice/water and stirred for 30 min, which precipitated crude SEX. The crude SEX was filtered, washed with water, and dried over P_2O_5 in vacuo, yielding 6.5 g (80%) crude SEX. Proton NMR analysis of the product indicated the following composition: 38% DADN, 51% SEX, 11% HMX. To date purification of this mixture has remained inadequate.

Optimum Batch Conditions for the Preparation of SEX: Oleum Nitrolysis

DADN (100.0 g, 0.138 mole) was dissolved in 750 mL of 100% HNO_3 at 20°C. With cooling (dry ice/acetone bath), 165 mL of 30% oleum was added at such a rate that the temperature of the mixture did not exceed 25°C. At the end of the addition, the flask was stirred at room temperature for 19.5 hours. The mixture was then poured into ice/water and stirred for 30 min, which precipitated the crude SEX. The precipitate was filtered, washed with several large portions of water, and dried over P_2O_5 in vacuo, yielding 45.2 g (38%) SEX. Analytical HPLC of the product indicated the following composition: 14.2% DADN, 84.0% SEX, 1.8% HMX.

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